IONIC SILVER:
TOXICITY and WEIGHT of the EVIDENCE

Melba S. Morrow, DVM
Antimicrobials Division
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Purpose

The purpose of this paper is to determine the applicability of the current regulatory advisories for silver in conducting risk assessments for pesticidal products intended for use on food contact surfaces and for non food uses. The advisories are based on studies and information which appeared in the literature and represent a departure from the traditional use of guideline laboratory animal studies in selecting endpoints for evaluating health hazards. The Antimicrobials Division has used an interim policy for evaluating the health effects of silver which employs the use of regulatory advisory levels established both by the Office of Water and through the Agency's Integrated Risk Information System (IRIS). The same study was used by both for establishing exposure limits for the antimicrobial uses of silver. This paper will set forth a rationale, based on observations in laboratory animals and humans, to address the Antimicrobials Division's belief that this interim approach is applicable. This paper will also address why additional laboratory animal data would not provide beneficial information which can be used in the determination of toxicological endpoints for assessment of human health.

Background

Silver ions and preparations containing silver in an ionic state have been used for over a century for medicinal and bactericidal purposes. Because of its bactericidal properties, silver has been used as a topical treatment for burns, as a treatment for venereal diseases, as an ingredient in cosmetic formulations and in the sanitation of swimming pools and hot tubs/spas. Silver has also been used in dentistry (as amalgams and as an ingredient in mouth washes), in acupuncture, jewelry- making and photography. Silver can be found in electroplating materials as well as in paints and in water purification systems. Safe levels for exposure to silver have been established by several regulatory Agencies, including the FDA, OSHA and EPA. Humans are exposed to silver by oral, dermal or inhalation routes; however, there is documented evidence that healthy humans have an average silver content in their tissues and organs that is approximately equal to 0.05 ug/kg. Although background levels of silver are present in normal, healthy humans, silver has no known physiological function in the human body.

The Agency has acknowledged that the risk assessment process for metals may be somewhat different than the risk assessment for other pesticides. In the ***Framework for Metals Risk Assessment*** document dated March 8, 2007, and developed under task from EPA's Science Policy Council, the Agency takes the position that specific approaches which have been used in conducting quantitative risk assessments for organic compounds may be outdated or may require modification to reflect the best available science. This rationale for modifying risk assessments for metals is based on the fact that metallic compounds possess unique attributes. Based on the information available in the literature and through studies involving animals and humans, AD has modified the approach to

conducting a risk assessment for silver. AD's approach is based on the information that currently exists in the literature and takes into consideration the values that have been determined by other offices in regulating silver relative to human exposure and risk.

REVISED APPROACH for ENDPOINT DETERMINATION

The toxicity of silver is well understood based on epidemiological data from humans, toxicology data in animals, and documented information on the metabolism of silver in mammalian species. All of these sources contribute to the knowledge the Agency has on the effects of silver in humans and thus allows the Agency to take a more integrated, science based approach in conducting a risk assessment for silver. Unlike other pesticides, silver does not have a conventional check-list of guideline laboratory animal studies to assess human risk. Based on our experience with the extensive use of silver and our historical knowledge of the compound, it is apparent that humans and laboratory animals do not handle elevated doses of silver in the same manner. For this reason, additional conventional laboratory animal toxicity studies would not provide a better understanding of the effects of silver in humans. The Agency has determined that silver and several of its salts (chloride, sulfate, nitrate and acetate) would be reviewed together and that the data could be used due to the fact that these silver salts react similarly in aqueous media and the major active ion is the silver ion.

A human biomonitoring study conducted in 1935, as reported by Gaul and Staud, has served as the basis for establishing regulatory limits for silver in drinking water and in the diet. The results from this study were further supported by the results from an inhalation study conducted by Pillsbury and Hill in 1939, which established inhalation limits for silver in humans. In both studies, the effect of concern was argyria, a bluish discoloration of the skin. Argyria, while a permanent condition is considered a cosmetic condition. The function of the skin as an organ is not compromised and the resulting discoloration is not associated with systemic toxicity. In the 1935 study by Gaul and Staud, silver was administered for medicinal purposes to 70 patients for periods from 2 to 9 years. Of the 70 patients receiving medicinal silver, 1/70 developed argyria after receiving an intravenous dose of 1 gram. This intravenous dose was converted to an oral dose of 0.014 mg/kg/day and was considered a lowest observed effect level. Other patients did not develop argyria until doses 5 times higher were administered. This study and an inhalation biomonitoring study by Pillsbury, et al, clearly determined the endpoint of concern for humans. Interestingly, the skin form of argyria has not been reported in laboratory animals when doses that are approximately 4 orders of magnitude higher (100 mg/kg) are administered.

These studies serve as the basis for regulatory advisories established for silver by the Office of Water (SMCL) and dietary limitations (reference dose) established under IRIS and for 8 hour inhalation exposure limits set by OSHA.

Further support for not requiring additional laboratory animal studies for silver is provided from the results of the developmental toxicity study in rats, conducted by the National Toxicology Program (NTP). In a developmental study conducted in 2002, silver

acetate was administered by gavage on days 6 – 19 of gestation. No developmental effects were reported at doses up to 100 mg/kg; maternal animals were observed to have piloerection and rooting behavior at 30 mg/kg. The observed effects in maternal animals would not be expected to occur in humans and are frequently observed in animal studies. These observations, when made in the absence of other clinical findings are not considered when establishing a "no adverse effect level". More importantly, the results from this study did not demonstrate an increased susceptibility of offspring, nor did it demonstrate systemic toxicity. This study corroborates the use of the information provided by the human biomonitoring study in determining dietary limits for silver and further supports our decision to not rely solely on animal data when assessing the health effects of silver in humans.

In addition to the information gleaned from the biomonitoring studies and the developmental toxicity study, the acute oral toxicity studies that have been provided to support the registration of silver as an antimicrobial agent establish LD_{50}s between 2000 and 5000 mg/kg. These values are above the limit dose for acute toxicity. For other silver salts the LD_{50} values may be variable based on the molecules to which the silver ions are attached. For antimicrobial silver salts, where the salts are similar and the data can be used interchangeably, the LD_{50} ranges are tighter as the silver ions drive the toxicity.

Finally, the pharmacokinetics of silver is understood and may explain the low systemic toxicity of the compound. The pharmacokinetics, which simply describes what the body does to a chemical when it is introduced into the body, would involve the metabolism, absorption, distribution and elimination of silver. Silver, when introduced to the body by the oral route undergoes a first pass through the liver. This first pass effect results in biliary excretion and the ultimate elimination through the feces of any absorbed silver. This first pass effect also reduces the potential for systemic distribution of silver to body tissues. In the human body, silver is not extensively metabolized and will react with proteins by binding to specific chemical groups contained in the structure of proteins (sulfhydryl, amino, carboxyl, phosphate and imidazole groups). Approximately 90% of administered silver is excreted in the feces. Many of the silver salts that are used as antimicrobial agents are insoluble and the bound fraction (approximately 10%) forms silver-protein complexes, which further remove silver from circulation. At elevated doses, the pathways of elimination become saturated and deposition of these complexes in the tissues is increased. The formation of these complexes and deposition in the skin, mucous membranes and conjunctiva are the primary mechanisms which result in the development of argyria. Based on information from biomonitoring studies, the lowest observed effect level for the formation of argyria was 1 gram (total dose), which was converted to an oral dose of 0.014 mg/kg/day.

Based on the information available for silver, regulatory offices within EPA, other federal agencies and international organizations have established safe levels for regulating silver in food water and air. These organizations have relied on the use of the Gaul and Staud (1935) or Pillsbury and Hill (1939) studies and have concluded that argyria is the endpoint of concern for humans exposed to silver. By regulating to prevent this effect, a

certain degree of protection is provided for the population from other toxicologic risks from silver that would be expected to occur at much higher levels. However, as our knowledge base increases and if it is necessary, the Agency may request additional studies to address human health concerns that may arise from dietary, occupational and residential exposure to silver.

TOXICOLOGY PROFILE

Information in this section has been extracted from the various literature reviews that have been conducted by various non-regulatory agencies. It is noted that although comprehensive literature searches have been conducted, there is no detail provided on the manner in which many of the studies were conducted or whether these studies would meet guideline requirements that the Agency has in place. The following is an overview of what the literature offers us on silver and its effects in humans through use experience and in laboratory animals.

Humans

The most commonly encountered health effect associated with long term exposure to silver is the development of the condition, argyria. Argyria has been described as blue-grey discoloration of the skin, which occurs predominantly in the areas of the body that have been exposed to direct sunlight, such as the face, neck and the back of the hands. The discoloration that occurs with argyria is permanent, but it has been characterized as being more of a cosmetic/disfiguring condition than one of toxicological significance. The physiological function of the skin is not compromised, only the color is changed. In this condition, silver is absorbed into the circulatory system and forms complexes as a result of its reaction with proteins. (Silver binds with sulfhydryl, amino, carboxyl, phosphate and imidazole groups). In the presence of sunlight, the complexes are acted upon to form a silver compound which is oxidized and bound to tissues as silver sulfide. It is believed that the silver sulfide, or in some cases, silver selenide, complexes stimulate melanin production, leading to the development of the blue-grey pigmentation change. Argyria can be either local, affecting the skin and the eyes, or general, affecting organs in the body in addition to the skin and eyes. One article on argyria has discussed the possibility that the presence of argyria may be a mechanism of detoxifying the effects of silver on other organs, by causing the silver to be sequestered in the tissue by way of forming silver-protein complexes. These silver complexes would decrease the circulating silver ions that would be available to cause adverse effects on other organs.

In humans, at elevated doses and over chronic periods of exposure, silver was associated with clinical symptoms relative to damage to the gastrointestinal tract. Exposure to high doses of silver has been associated with abdominal pain, diarrhea, and vomiting. The lethal dose of silver nitrate has been reported to be greater than 10grams in humans although there have been reports of humans surviving doses in excess of 10 grams.

Animals

The toxicity of silver has been well documented in the literature, and in spite of the fact that acceptable guideline studies do not exist to address each facet of toxicity; regulatory decisions have been based on documented accounts of the toxicity when administered to man and to laboratory species by various routes. These resources include published documents from the Agency for Toxic Substances and Disease Registry (ASTDR), the World Health Organization (WHO), internally reviewed studies and documents from IRIS and from the Oak Ridge Environmental Restoration Program, the current RED for silver and other internal documents which address regulatory advisories for silver.

Interestingly, there is no animal condition that would mimic the dermatologic form of argyria found in humans following exposure to silver by various routes. This may be due in part to the protection imparted by the presence of the fur or by the fact that laboratory animal species are not routinely exposed to direct sunlight. Argyrosis, a form of argyria which involves silver deposition in organs has been documented. In laboratory species, the effects of silver toxicity have been reported to involve pathology to the liver (necrosis) and kidney (thickening of the basement membranes of the glomeruli), and at elevated levels, death.

The following information has been gleaned from the available literature and from mammalian studies evaluated in various regulatory data bases. A profile of the toxicology information from literature and from submitted data appears in Table I.

Metabolism

Silver is absorbed by the dermal, oral and inhalation routes. It is excreted primarily in the feces with small amounts being excreted in the urine. The distribution of silver following absorption appears to be dependent on the route of administration. This is also true for the excretion. Following oral administration of silver, the material undergoes a first pass through the liver, where it is subjected to biliary excretion. This results in a somewhat reduced systemic distribution of silver. Following oral administration of silver, the compound is distributed to the reticuloendothelial organs (liver, spleen, bone marrow, lymph nodes), the skin and the kidneys. When silver is inhaled, the distribution is primarily to the lungs, liver and blood.

Oral doses are excreted more quickly than inhaled doses. Retention of silver following exposure also appears to be species dependent. Results from one study, report a 98-99% fecal recovery of an orally administered dose of silver after only 2 days following dosing in rats and mice. For inhaled doses of silver, there was a reported 90% fecal recovery within 30 days of exposure in dogs. Results reported by East, et al (1980) and McIntyre et al (1978) stated that following a single oral dose of silver, rats retained silver at a rate that was 10% greater than the amount retained by dogs.

Acute Toxicity

According to the literature, the acute toxicity of silver compounds, based on LD_{50} values appears to be slight to moderate and the level of toxicity is dependent on the route of administration, the animal species and the type of silver that is tested. In one study, the oral LD_{50} in mice for colloidal silver and for silver nitrate are 100 mg/kg and 129 mg/kg, respectively. In another study in mice, 50 mg of silver nitrate caused death in 50% of dosed animals over a 14 day observation period. In dogs, colloidal silver was lethal at a 500 mg dose. The oral LD_{50} for rats, when tested with silver cyanide was 125 mg/kg. In rats, an LD_{50} of 2820 mg/kg was reported for silver oxide, a relatively insoluble compound, while the LD_{50} for silver nitrate in rats was 1173 mg/kg. AD's in-house data for registered products, reported LD_{50}s between 2000 - 5,000 mg/kg.

When administered by routes other than oral, toxic effects were variable. Following an intraperitoneal (IP) injection of silver nitrate at 0.216 grams (approximately 216 mg/kg), fatalities were reported in six of the ten treated guinea pigs. In rabbits, a 20 mg/kg IP injection of silver nitrate resulted in death, which was accompanied by observed degeneration of the liver parenchyma and the kidney tubules. Seven milligrams of silver nitrate administered subcutaneously affected testicular histology and spermatogenesis. Contact dermatitis and generalized allergic reactions have been reported in humans repeatedly exposed to silver by the dermal route.

Sub Chronic Toxicity

Following a 12-week administration of silver nitrate in a 0.25% solution, silver was deposited in the glomerular (kidney) basement membranes. At doses of 1500 ppm, silver acetate in water resulted in liver necrosis and death in rats after a 2 to 4 week exposure period. Silver acetate, administered in the diets at doses ranging from 130 -1000 ppm to rats, was associated with hepatocellular necrosis and muscular dystrophy.

Chronic Toxicity

In a study conducted for 6-12 months, rats were administered silver via drinking water. At 2 mg/L, there was a reported decrease in the nucleic acid level in the brain and the liver. A No Effect Level (NOEL) was reported to be 0.5 mg/L. In rabbits administered silver in the drinking water for 11 months a No Adverse Effect Level (NOAEL) was established at 0.0023 mg/kg, based on the occurrence of brain abnormalities in the nervous, vascular and glial tissue of the encephalon and the medulla at a dose level an order of magnitude higher (0.023 mg/kg). The abnormalities were not specified as to type and incidence

(It is pointed out that the dose levels for some acute, subchronic and chronic toxicity studies were extracted from the literature and the details surrounding the conduct and evaluation are not available).

Reproductive/Developmental Toxicity

It has been documented that silver, when administered to rats, has the ability to cross the placenta and it has been detected in the liver and brain tissue of rat fetuses. This finding was reported by Danscher 1981 and Rungby and Danscher in 1983. A 2002 study summary, derived from an NTP report, concluded that the no **adverse** effect level (NOAEL) recorded for developmental toxicity in rats receiving gavage doses of silver acetate, was greater than100 mg/kg when the test material was administered on gestation days 6 through 19. No increase in susceptibility was apparent in this study. Effects were reported in maternal animals at 30 mg/kg but these were effects that would not be expected to occur in humans (piloerection and rooting); therefore the NOAEL for maternal animals was also set at 100 mg/kg.

Carcinogenicity

Data required to evaluate the carcinogenic potential of silver to man and animals are not available. Under an earlier system of classifying chemicals with regard to their carcinogenicity, silver was placed in Group D. A "D" classification implies that there are no data available from any study which could address the carcinogenicity of silver.

TABLE 1
Ionic Silver: Oral Toxicity Profile (from literature and data reviews)

Study/Species	Dose, NOAEL, LD_{50}s	Observed Effects
Acute		
Mouse (LD_{50})	129 mg/kg	
Rat (LD_{50})	125 mg/kg; 2820 mg/kg, 1173 mg/kg 2000-5000 mg/kg (in house studies to support registration)	
Subchronic		
Rat (2-4 wks)	1500 ppm (150 mg/kg)	Liver necrosis and death
Rat (12 wks)	0.25% solution	Deposition in glomerular basement membrane.
Rat	130-1000 ppm (13- 100 mg/kg)	Hepatocellular necrosis and muscular dystrophy
Mouse (4 mos)	18 mg/kg	hypoactivity
Chronic (6 -12 mos.)		
Rat	2 mg/L – LOAEL (0.5mg/L -NOAEL)	Decreased nucleic acid levels in brain and liver
Reproductive/Developmental*		
Rat (developmental) Maternal	NOAEL > 100 mg/kg NOAEL = 100 mg/kg	No adverse effects observed Body weight loss (< 10% at highest dose tested), piloerection, rooting
Carcinogenicity	Classified as "D"	No data available
Metabolism		
Rat	98-99% recovery after 2 days (oral doses)	
Dog	90% recovery within 30 days of exposure (inhaled doses)	

* Study conducted by NTP, using silver acetate (2002)

Interim Policy and Application of Additional Safety Factor

In June of 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met to discuss the adequacy of the toxicology database for silver. Data were referenced from the 1993 Reregistration Eligibility Decision (RED) document, and were based solely upon open scientific literature. HIARC concluded that the studies cited in the RED were inadequate for hazard identification and risk assessment.

On September 8, 2004, members of the Antimicrobials Division Toxicity Endpoint Committee (ADTC) met again to discuss toxicology issues with respect to silver. ADTC discussed this issue using the available information on the hazard (updated database) and the chemistry of the silver compounds under consideration. For purposes of hazard characterization and endpoint selection for risk assessments involving elemental silver and silver salts, the ADTC concluded that silver salts can be treated together as a class. Once internalized to the body, the compound of interest is ionic silver, which is common to the silver salts. Therefore, one toxicology dataset can represent the hazard for the silver salts.. The Risk Assessment and Science Support Branch (RASSB) was asked to prepare interim end-points for risk assessment which were to be used in the absence of a complete toxicological data set. Since this meeting in 2004, the developmental toxicity of silver was addressed in a study performed at the National Toxicology Testing Program (NTP), and based on the results there was no developmental toxicity associated with silver at doses up to and including 100 mg/kg.

The silver endpoint of concern, argyria, is one that occurs after chronic exposure and one which has not been reported in animal studies. AD has used this endpoint for regulating and evaluating the hazard associated with silver based on other Agency-wide advisories posted for this chemical and supporting documentation on the toxic effects of silver in humans. Both the Secondary Maximum Contamination Level (SMCL) reported by the EPA's Office of Water and the oral reference dose (RfD) reported under the EPA's Integrated Risk Information System (IRIS) were determined based on the results from a human biomonitoring study reported in the Journal of the American Medical Association in 1935 by authors L.E. Gaul and H.E. Staud. Argyria was reported following intravenous doses as low as 1 gram. The results from this study, which covered a period up to 9 years and involved a total of 70 patients, were used to determine a Lowest Observed Adverse Effect Level (LOAEL) which was converted into an oral equivalent dose of 0.014mg/kg/day. For SMCLs additional mathematical derivations were applied to obtain a 0.1 mg/L dose level. The factors applied for changing volume to mass account for the slight difference in the values reported for the SMCL (0.003 mg/kg/day) and for the RfD (0.005mg/kg/day).

A safety factor of 3 was applied instead of the usual 10X for interspecies variability to the oral scenario based on the following rationale as reported by the Office of Water and IRIS. First, the critical effect was cosmetic and not of toxicological significance. Second, the derivation of the LOAEL included the most sensitive individual, since other patients did not present with argyria until dose levels five (5) times higher were administered. Finally, in the human bio-monitoring study, silver was administered to these individuals over a period of time which is in excess of chronic exposure and which

approaches a level which would be considered a lifetime exposure rate. Therefore, the dose that was administered was determined as being one which would mimic lifetime exposure.

For oral exposure route, AD continues to use the drinking water Secondary Maximum Contaminant Level (SMCL) level of 0.1 mg/L (0.003 mg/kg/day) based on skin discoloration and graying of the whites of eyes (argyria), and applied an additional safety factor of 3 to address the residual uncertainty associated with the missing reproductive, neurotoxicity and chronic toxicology studies. An additional safety factor of 3 instead of 10 was applied for the presence of data gaps and was based on knowledge of historical data and uses for silver.

$$\text{Oral Interim Endpoint} = \frac{0.003 mg/kg/day}{3} = 0.001 mg/kg/day$$

For Inhalation Exposure, RASSB decide to use the on OSHA 8-hour TWA of 0.01 mg/m^3 (0.001 mg/kg/day) based on argyria and applied an additional safety factor of 3x to address the residual uncertainty associated with the missing reproductive, neurotoxicity and chronic toxicology studies. A safety factor of 3 instead of 10 is used based on historical data for silver.

$$\text{Inhalation Interim Endpoint} = \frac{0.001 mg/kg/day}{3} = 0.0003 mg/kg/day$$

For Dermal Exposure, silver ion tends to bind to the skin and do not penetrate the skin to cause systemic effects. Skin discoloration is the only concern for silver exposure through the dermal route. The dermal risk assessment for silver uses the drinking water SMCL level of 0.1 mg/L (0.003 mg/kg/day), without any extra safety factor.

$$\text{Dermal Interim Endpoint} = \frac{0.003 mg/kg/day}{1} = 0.003 mg/kg/day$$

Summary

Based on the information that is available through the literature and our product files and from other scientific research sources the following can be stated about our knowledge of the toxic effects of silver:

- Silver has been used in a variety of settings that result in human exposure for over a century.
- Argyria is the most common effect reported in humans following exposure to elevated levels of silver.
- Argyria is not of toxicological significance because it does not adversely affect the function of the skin; however, it is a permanent condition.
- Argyria is believed to provide protection to individuals by preventing silver from entering circulation and being deposited in other body tissues.
- Argyria has not been reported in animal studies following prolonged exposure at elevated dose levels
- The Office of Water (OW) and IRIS have established allowable limits for silver in food and water which safeguard against the occurrence of argyria
- The levels established by OW and IRIS are much lower than the dose levels that have been associated with toxicity (based on liver and kidney pathology) in laboratory animals.
- A developmental study in rats conducted by NTP did not demonstrate that there was any susceptibility of newborn animals to the toxic effects of silver.
- A side-by-side comparison of effect levels in humans and in animals demonstrates that use of the currently established regulatory advisories is a more conservative approach to protecting the general population from the effects of silver over-dosing.(See Table 2)
- AD has allowed for the use of an additional safety factor to address missing laboratory animal studies to assess reproduction, chronic toxicity and neurotoxicity even though the literature contains information to address toxicity for some of these exposure scenarios.
- Additional laboratory animal studies, while providing data will not result in endpoints that will protect against argyria based on the dose at which adverse effects occur.
- In the event that the state of the science changes, EPA can request additional data to address human exposure.

TABLE 2
Comparison of Regulatory Advisories* to NOAELs/LOAELs for Silver

Regulatory measurement	Advisory Level	AD Adjusted Level (3x UF)	No Adverse Effect Levels (NOAEL) mg/kg			
			Acute[1] (LD_{50})	Subchronic[2]	Neuro-toxicity[2]	Devel-opmental[3]
RfD	0.005 mg/kg/d	0.0016 mg/kg/d	2000-5000	13-150	18.1	100
SMCL	0.003 mg/kg/d	0.001 mg/kg/d				
OSHA/TWA	0.001 mg/kg/d	0.0003 mg/kg/d				

* Regulatory Advisories were derived from a lowest observed adverse effect level LOAEL) and not a no adverse effect level (NOAEL).
1 - LD_{50} values as reported for silver products currently registered by AD
2 - NOAELs from literature citations
3 - Developmental Toxicity conducted by NTP

Conclusions

It should be kept in mind that silver is not toxic at the regulatory advisory levels and that the endpoint that is being used for regulatory purposes is not one that is toxicological in nature. With the scientific support and documentation that argyria is not of toxicological concern and that quantified limits for silver exposure can be established to prevent the occurrence of this cosmetic event, it may be necessary to regulate silver outside of the scope that other chemicals, which have toxic endpoints, are regulated. It is evident from the dose levels and toxic responses that are available for laboratory species, that regulation based on animal data will not provide the level of protection against the manifestation of argyria. This is based on the fact that the dose levels for toxicity in animals are orders of magnitude greater than the levels that EPA and other agencies have established as being acceptable and protective for the permanent cosmetic effect caused by exposure to elevated levels of silver. The use of laboratory animal studies in this case would not be protective against the occurrence of argyria, which by its own nature may be a protective indicator that toxic levels are being approached.

Based on the information available for silver, it is AD's position that a more conservative estimation of risk is accomplished by using the regulatory advisories that have been established. The requirements for FQPA are not applicable in this case because there is no difference in the effects of silver that are age related. In addition, the developmental study has provided information which demonstrates that there is no age-related susceptibility to the effects of silver. Furthermore, argyria is not a toxic or harmful effect as it involves discoloration and does not compromise the function of the skin. Finally, the regulatory advisories provide safe levels of oral silver exposure and by applying an additional safety factor to these acceptable limits AD has provided an additional three-fold margin of protection.

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NOTE: The information sources for this paper are provided below; however, each of the sources has its own extensive list of resource materials which were consulted in the development of the individual documents.

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